IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:

Applicants:	Finkelman *et al.*	:	Case No.	91830/625
Serial No.	09/167,088	:	Examiner:	G. Gabel
Filed:	October 6, 1998	:	Art Unit:	1641

Title: METHODS FOR MEASURING IN VIVO CYTOKINE PRODUCTION

The Assistant Commissioner of Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR 1.132

1. This declaration under 37 CFR Sec. 1.132 is supportive of the Response and Amendment filed herewith.

2. I, Fred Finkelman, M.D., have been employed by the University of Cincinnati since 1995 and that from 1995 to the present time I have been, and still am, engaged in a research program in the field of immunology and particularly cytokine biology;

3. I have reviewed the 13 September 2000 Office Action in the above captioned case and I am familiar with the references, Tamarkin *et al.* (US 5,328,899), Pouletty *et al.* (US 5,612,034), and David *et al.* (US 4,486,530), cited by the Examiner.

4. I disagree with the Examiner's position and maintain that one of ordinary skill in the field of immunology and medical science would not deduce the present invention upon reading the references cited by the Examiner, either alone or in combination.

5. The assay disclosed by Tamarkin reference is a competitive binding assay that measures the ability of an analyte present in a serum sample to block the binding of biotin-labeled analyte to the plate. The assay measures the total of bound and unbound analyte present in a biological fluid. If the analyte is one with a short biological half-life and is not bound by endogenous serum proteins, the Tamarkin assay binding protein would not contact the analyte at all since it would be used up too quickly in the biological system. If endogenous serum proteins bind the analyte, then the methods of the Tamarkin reference would measure some product of the quantity of the analyte and quantity of analyte binding protein produced over an unknown period of time.

Differences in the quantity of analyte measured in two samples might reflect differences in quantity of analyte binding protein in the samples rather than quantity of analyte produced.

6. Tamarkin differs from the claimed process in that it is a competitive binding assay using polyclonal antibodies adhered to a plate to measure the ability of an analyte present in a serum sample to block the binding of biotin-labeled analyte to the plate. The Tamarkin reference teaches using a single, polyclonal antibody, not two specific binding molecules (preferably monoclonal antibodies); it is not utilized in vivo to obtain the specific amount of analyte excreted over a fixed period of time; it does not teach using an excess of binding molecule; and it does not teach using a neutralizing binding molecule that binds the analyte to form a targeting moiety:target analyte complex that prevents the analyte's catabolism, excretion, or binding to its respective receptor.

7. Pouletty *et al.* teaches only that one can increase the in vivo biological half-life of a compound that normally has a short in vivo half-life by injecting it into an animal so that it binds covalently to a molecule that naturally has a long in vivo half-life. Pouletty does not suggest that increasing the half-life would provide the results of the present invention by using an excess of a neutralizing binding molecule that prevents catabolism.

8. David *et al.* teaches only that a two-site or sandwich type assay may be used to determine the presence and concentration of an antigen. There is no mention or suggestion that such an assay may be used to determine analyte production *in vivo*.

9. In my opinion, one of ordinary skill in the field of immunology and medical science would find nothing in Tamarkin, Pouletty, or David, alone or in combination that would teach or suggest the present invention or any reason for making it.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Fred Finkelman, M.D.

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Fred Finkelman, M.D.

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